Megaloblastic Anemia

Associated with Surgically Produced Gastrointestinal Abnormalities

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• Two of the mechanisms for vitamin B_{12} deficiency, leading to megaloblastic anemia, are the result of surgically produced abnormalities of the gastrointestinal tract. The basic mechanism is different for each lesion.

Total gastrectomy results in complete lack of intrinsic factor which is necessary for vitamin B_{12} absorption. It is believed that if patients survive long enough and are not given prophylactic vitamin B_{12} therapy, all would develop megaloblastic anemia.

Intestinal anastomosis leading to stasis of intestinal contents, with overgrowth of bacteria may cause vitamin B_{12} deficiency through bacterial interference with the utilization of vitamin B_{12}.

Use of radioactive vitamin B_{12} (cobalt^{60}-labeled B_{12}) has led to a better understanding of the pathogenesis of both types of megaloblastic anemia. The radioactive vitamin provides a useful tool for study of its absorption from the gastrointestinal tract.

THE OBSERVATIONS of Minot[14] in 1926 that hematologic improvement occurred in patients with pernicious anemia who were fed large amounts of liver started a series of investigations to determine the mechanisms involved in this fundamental clinical discovery. As a result of extensive clinical and biochemical studies over the succeeding 25 years it has been established that hematopoiesis is concerned with nucleoprotein metabolism, and that the vitamins, folic acid, ascorbic acid and vitamin B_{12} are all involved in very complex interrelationships concerned with nucleic acid chemistry.

Megaloblastic anemia may occur as a result of several fundamentally different mechanisms whereby a deficiency of either folic acid or vitamin B_{12} is brought about. Two of these mechanisms, both of which are incident to surgical operations on the gastrointestinal tract, will be dealt with in this presentation. Megaloblastic anemia may result from total removal of the stomach, and it may also occur after operations on the intestine where a blind loop of bowel is produced in association with intestinal anastomosis. When megaloblastic anemia occurs after either of these two surgical procedures, it is usually the result primarily of a deficiency of vitamin B_{12} rather than of folic acid. In most of the reported cases, pronounced reticulocyte responses occurred upon treatment with vitamin B_{12} parenterally. However, the mechanism whereby vitamin B_{12} deficiency occurs is a basically different one for each of the two surgically produced abnormalities. Although megaloblastic anemia resulting from total gastrectomy, or from the formation of an intestinal blind loop, is a rare occurrence, special studies with a few cases have thrown new light on the pathogenesis of the anemia in each instance and have contributed somewhat to understanding of hematopoiesis in general.

A valuable tool became available with the report of Heinle and co-workers[9] that cobalt^{60}-labeled vitamin B_{12} could be used to trace the absorption of this vitamin from the intestinal tract. Using a method whereby fecal excretion is measured after oral administration of 0.5 microgram of radioactive vitamin B_{12}, the author studied its absorption in 12 patients who had had a total gastrectomy and in three patients who had megaloblastic anemia associated with intestinal anastomosis and blind loop formation.

MEGALOBLASTIC ANEMIA FOLLOWING TOTAL GASTRECTOMY

Castle's[4] experiments 25 years ago led to the concept that pernicious anemia is caused by deficiency of a gastric or "intrinsic" factor. Normally this reacts with a food or "extrinsic factor," and this reaction is necessary for normal erythrocyte formation. The extrinsic factor is now known to be vitamin B_{12}. The nature of intrinsic factor is not yet known precisely, although extracts of hog stomach mucosa[18] have now been fractionated and concentrated to such an extent that as little as 2 mg. mixed with vitamin B_{12} will result in a hematopoietic re-

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TABLE 1.—*Absorption, in persons used as controls, of 0.5 microgram of orally administered cobalt^{60}-labeled vitamin B_{12}, as measured by subtracting fecal excretion from the oral dose.*

Case No.	Age	Diagnosis	Absorption Per Cent
1	37	No disease	59
2	64	Arteriosclerosis	74
3	31	No disease	80
4	48	No disease	70
5	48	Hypogonadism	71
6	32	No disease	67
7	45	Obesity	55
8	51	Dystrophia myotonia	67
9	30	No disease	68
10	34	Reiter's syndrome	81
11	24	Rheumatoid arthritis	43

Average absorption = 68 per cent

sponse when given orally to a patient with pernicious anemia in relapse. The exact mechanism whereby intrinsic factor exerts its effect is not known with certainty, but all the evidence indicates that it is necessary to enable vitamin B_{12} to be absorbed across the intestinal membrane.

Since 1929 a controversy has existed as to the site of origin of the intrinsic factor in man. It is known that in swine it occurs in the duodenum as well as the stomach, and for this reason it has long been thought by many hematologists to be present there in man, perhaps being secreted by Brunner's glands. This belief was strengthened by the fact that pernicious anemia does not develop in many patients who have had total gastrectomy, although it might be expected to develop in every case of total extirpation if the intrinsic factor were secreted nowhere but in the stomach.

Recent experiments[9] with radioactive vitamin B_{12} have shown that patients with pernicious anemia do not absorb it. Essentially the entire test dose can be recovered in the stools. However, when it is administered with normal human gastric juice, absorption becomes perfectly normal. The author also has noted these phenomena (Chart 1).

Absorption of vitamin B_{12} in a normal person is very limited. No matter how large a dose is given not much more than 1.5 micrograms can be absorbed.[18] In studies by the author it was observed that with a test dose of 0.5 microgram of cobalt^{60}-B_{12} the average amount absorbed in 11 persons was 68 per cent, the greatest absorption being 81 per cent and the lowest 43 per cent (Table 1). Almost identical data were reported by Callender, Turnbull and Wakisaka.[1] The reason for this extreme limitation of absorption of vitamin B_{12} is not yet known.

In studies of 12 patients who had had total gastrectomy[7, 19] it was noted that they had absorption of radioactive vitamin B_{12} almost identical with the absorption of patients with pernicious anemia. In every instance essentially the entire test dose of 0.5 microgram could be recovered in the stools. When normal human gastric juice was given with it, normal absorption occurred (Chart 2). Similar observations were made by Callender and co-workers[2] and by Ley.[10] Thus it appears that the site of origin of intrinsic factor in man is limited to the stomach. If it were produced in the duodenum or elsewhere in the gastrointestinal tract there should be some absorption of vitamin B_{12} as measured by the fecal excretion test with cobalt^{60}-B_{12}. Furthermore, megaloblastic anemia should not occur after total gastrectomy.

However, anemia that is indistinguishable from Addisonian pernicious anemia may develop. Combined system disease may occur as well as the other symptoms. The condition of the bone marrow and of peripheral blood are those of pernicious anemia. Since patients who have had total gastrectomy do not absorb any vitamin B_{12} from dietary sources,

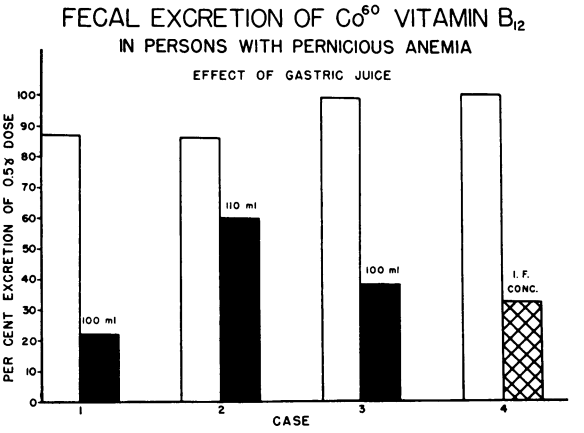

Chart 1.—Fecal excretion of cobalt^{60}-B_{12} in pernicious anemia (white columns), and the effect of normal human gastric juice (cases 1, 2 and 3), and of an intrinsic factor concentrate* (case 4), on excretion (black columns).

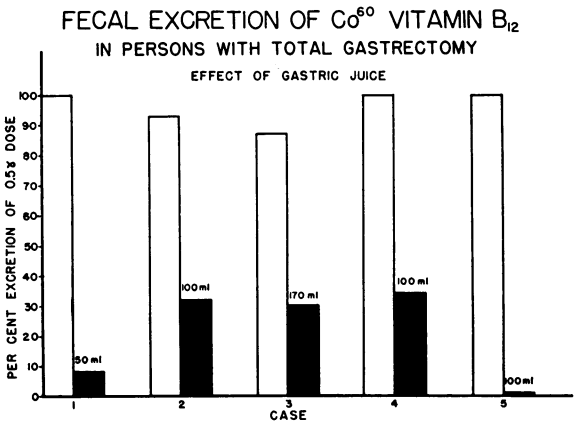

Chart 2.—Fecal excretion of cobalt^{60}-B_{12} in five patients who have had a total gastrectomy (white columns), and the effect of normal human gastric juice on excretion (black columns). Seven additional patients with total gastrectomy, similarly studied, showed identical patterns of excretion.

*Supplied by Dr. R. W. Heinle, Upjohn Company.

the question arises why megaloblastic anemia does not always follow total gastrectomy. There are four factors in the overall situation which adequately explain this paradox:

1. *Survival after the operation.* Total gastrectomy has been in wide use for only about ten years. The operative mortality rate is around 10 or 15 per cent, and survival longer than three years after operation for carcinoma (the indication in most cases) is about 20 per cent. Thus not many patients survive long enough for megaloblastic anemia to develop.

2. *Interval before development of anemia.* It may be that stores of vitamin B_{12} in the liver are sufficient for the patient's needs for several years. The daily human requirement of the vitamin is not more than 1.0 microgram. Assay of liver slices taken at autopsy showed that the human liver contains, on the average, about 1.2 milligrams of B_{12}[20]—enough to last almost four years. In pernicious anemia when therapy is stopped it has been shown that relapse may not occur for as long as three years.[15] Analysis of 46 cases of total gastrectomy by MacDonald and co-workers[13] revealed that megaloblastic anemia developed in 12. The anemia appeared four years or more after operation in nine of these cases.

3. *Completeness of gastrectomy.* Sometimes it is technically difficult to transect the cardiac end of the stomach above the cardioesophageal junction. Sometimes 1 to 2 cm. of cardia may be left in situ, yet the case be reported as one of total gastrectomy. Since in man the cardia is an active site of secretion of intrinsic factor a small amount left behind might provide an amount of intrinsic factor adequate for normal utilization of vitamin B_{12} contained in the diet.

4. *Prophylactic therapy.* It has been observed that even if prophylactic injections of liver extract or vitamin B_{12} are not advised by the surgeon, patients almost always receive multivitamin capsules. Many of these preparations contain folic acid, which would prevent megaloblastic anemia for some time. Many preparations now contain B_{12} and intrinsic factor concentrates. Only one of the 12 patients studied by the author had megaloblastic anemia but nine had received prophylactic therapy.

The patient with anemia was a 59-year-old man who had total gastrectomy in 1949 for carcinoma. Except for weight loss of 40 pounds which he could not regain he remained entirely well until September 1953, when he began to feel weak. Weakness progressed until the patient was admitted to the hospital in May 1954 with pronounced anemia. The hemoglobin content was 5.5 gm. per 100 cc. and erythrocytes numbered 1.39 million per cu. mm. There were no neurological abnormalities. The bone marrow

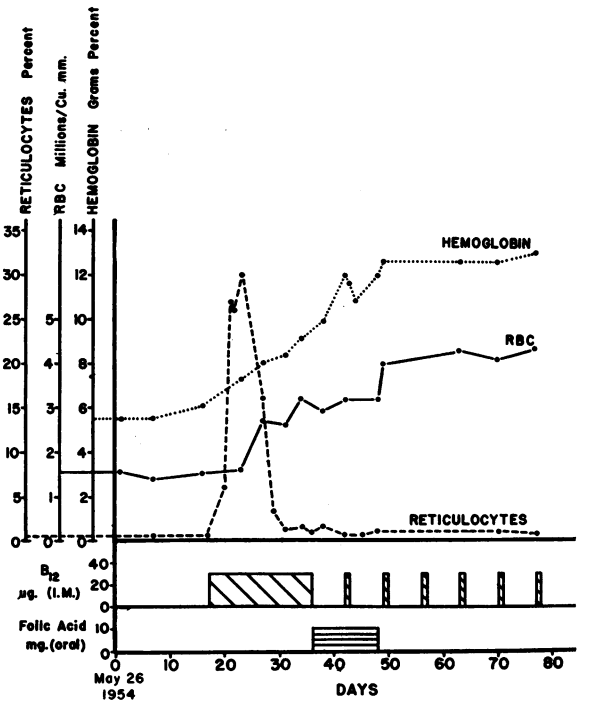

Chart 3.—Patient with severe megaloblastic anemia occurring four and a half years after total gastrectomy for carcinoma. Effect of vitamin B_{12} therapy on reticulocytes, hemoglobin, and erythrocytes.

was megaloblastic. The mean corpuscular volume was 109 cu. microns, mean corpuscular hemoglobin 35 micromicrograms per cell, and mean corpuscular hemoglobin concentration 32 per cent. A reticulocyte response of 30 per cent occurred on the sixth day of B_{12} therapy. Folic acid given later produced no additional response (Chart 3). Fecal excretion of cobalt^{60}-B_{12} was 95 per cent, but only 49 per cent was excreted when an intrinsic factor concentrate was administered with the test dose of radioactive vitamin B_{12}.

Considering the small number of patients who survive total gastrectomy long enough for megaloblastic anemia to develop, and considering the widespread use of antianemic medications, the rarity of megaloblastic anemia after the operation is not surprising. The evidence indicates, however, that every patient who does survive long enough and who does not receive prophylactic therapy will develop megaloblastic anemia indistinguishable from Addisonian pernicious anemia. An injection of 30 micrograms of vitamin B_{12} once a month would be adequate to prevent anemia indefinitely, and may be recommended as sound practice.

MEGALOBLASTIC ANEMIA ASSOCIATED WITH INTESTINAL ANASTOMOSES

In 1895 Faber[5] reported the case of a young woman in whom pernicious anemia was associated

with intestinal stricture. In 1929, Little, Zerfas and Trusler[12] found the characteristic clinical picture of pernicious anemia in a young man who had had several operations to cure an intestinal fistula following acute appendicitis. The operations resulted in anastomosis between jejunum and ascending colon, forming a blind loop of intestine and causing stasis of intestinal contents. Up to the present, reports of 79 cases can be found in the literature,[8] in which megaloblastic anemia is associated either with an intestinal stricture or surgically produced anastomosis which leaves a blind loop of gut. The common denominator appears to be the presence of an anatomical abnormality which causes stasis and stagnation of intestinal contents.

The anemia brought about in such cases is indistinguishable from Addisonian pernicious anemia. Glossitis, icterus and combined system disease have all been observed in this syndrome. However, both hydrochloric acid and intrinsic factor have been demonstrated repeatedly in the gastric juice. Thus the mechanism for the development of the anemia is not a lack of intrinsic factor as in pernicious anemia or the megaloblastic anemia of total gastrectomy. In many of the reports of recent cases it was noted that the patient responded to parenteral therapy with vitamin B_{12}. Surgical correction of the lesion that causes intestinal stasis may result in permanent cure of the anemia.

What the mechanisms are that bring about the anemia in such circumstances has been conjectural until recent years. One theory is that intestinal absorption is defective, as in sprue. However, steatorrhea is uncommon, and studies have demonstrated good absorption of fat and glucose. Thus it does not seem likely that this is the correct explanation. Beginning with Faber's case a luxuriant growth of bacteria throughout the small bowel above the stricture, or in the stagnant areas, has been noted often at autopsy. Faber suggested that the anemia was caused by absorption of a poison from the stagnant bowel contents. The anemia has been experimentally produced in dogs by bringing about intestinal strictures[16] and in rats after the construction of retroperistaltic blind pouches of small intestine.[3, 21] These observations indicate that intestinal bacteria have adverse effect on hematopoiesis.

With the advent of antibiotics it has been possible to investigate certain relationships between bacteria and hematopoiesis. Thus Lichtman and co-workers[11] obtained definite although suboptimal hematologic responses in pernicious anemia from aureomycin administration. In East Africa certain kinds of megaloblastic anemia were found to respond dramatically to oral administration of penicillin alone.[6] Finally two patients with megaloblastic anemia associated with intestinal anastomoses, studied in Finland, were treated with aureomycin and terramycin, and pronounced reticulocyte responses occurred.[17]

The author has observed three patients during the past year with megaloblastic anemia associated with intestinal stasis. Each had complete hematologic response to parenteral vitamin B_{12} therapy. Summaries of these cases follow:

CASE 1. A 19-year-old boy was admitted to Harbor General Hospital* with characteristic signs and symptoms of combined system disease and mild megaloblastic anemia. The anemia and all the neurological signs disappeared upon administration of vitamin B_{12}. At the age of ten the patient had had appendectomy followed by intestinal obstruction. He then had intermittent abdominal cramps until intestinal resection was performed at the age of 15. The exact nature of the anastomosis could not be ascertained. Following this the patient was entirely symptom-free until the anemia, with neurological disturbance, developed.

CASE 2. A 24-year-old Mexican man who worked in a hospital laboratory had several operations for intestinal obstruction and to correct internal fistulae which developed after appendicitis at the age of 13. The patient then was entirely well until ten years later, when weakness, pallor and soreness of the tongue developed. Studies revealed severe anemia and free hydrochloric acid in the gastric juice. Megaloblastosis was noted upon study of bone marrow aspirate. The patient was treated for six months with parenteral injection of B_{12} and symptoms were completely relieved. The injections were stopped and he remained well for 16 months. Then weakness and soreness of the tongue recurred. The patient was admitted to Wadsworth Veterans Administration Hospital in January 1954. Upon examination at that time, pallor and mild icterus were noted. Results of a neurological examination were within normal limits. The icterus index was 23 units at the time of admittance. Later it declined to 9 units. The result of an oral glucose tolerance test was normal. The hemoglobin content of the blood was 6.4 gm. per 100 cc. Erythrocytes numbered 1.8 million per cu. mm. and the packed cell volume was 19.5 per cent. The mean corpuscular volume was 108 cu. microns, the mean corpuscular hemoglobin 35 micromicrons and the mean corpuscular hemoglobin concentration 30 per cent. A barium study of the small bowel revealed dilated loops of ileum with stagnation of barium in the pelvic portion of the ileum for 24 hours. The patient was treated with vitamin B_{12}. Reticulocyte response of 16 per cent occurred and complete recovery ensued. At last report the patient was entirely well and was receiving 30 micrograms of B_{12} intramuscularly once a month.

CASE 3. A 60-year-old man had extensive diverticulosis of the entire small intestine. In 1949 a jejunal diverticulum perforated and a volvulus of

*Dr. Nancy Landon at Harbor General Hospital made possible the studies on this patient.

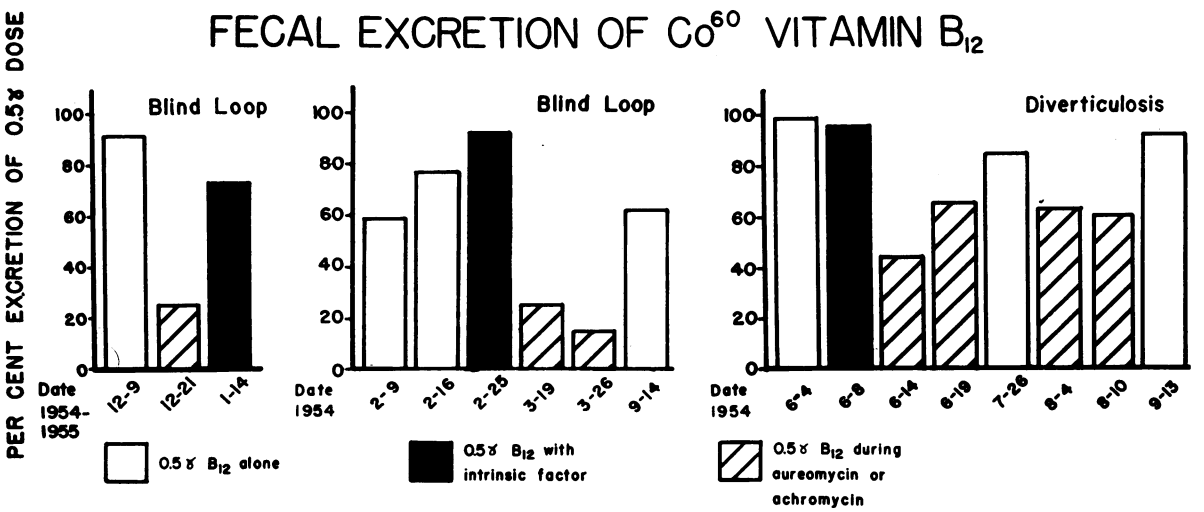

Chart 4.—Fecal excretion of cobalt^{60}-B_{12} in three patients with intestinal stasis. Two had blind loops, and one had diverticulosis of the small intestine. Note that excretion was very high. Intrinsic factor had no effect, but antibiotic administration resulted in significant decrease in excretion in all three.

the terminal ileum and cecum occurred. A resection of two feet of ileum with the cecum was performed, with end-to-side anastomosis of ileum to hepatic flexure. This resulted in a blind pouch of ascending colon.

In January 1952 the patient entered the hospital and was found to have mild macrocytic anemia. Upon examination of material from the bone marrow, megaloblastosis was noted. The hemoglobin content was 8.0 gm. per 100 cc. of blood, erythrocytes numbered 2.49 million per cu. mm. and the hematocrit 27 per cent. The mean corpuscular volume was 108 cu. microns, the mean corpuscular hemoglobin 32 micromicrons and the mean corpuscular hemoglobin concentration 30 per cent. Reticulocytes made up 0.4 per cent of total cells. There was free hydrochloric acid in the gastric contents. The stool did not contain an abnormal amount of fat. Treatment with vitamin B_{12} parenterally resulted in hematologic response, with reticulocytes increasing to 6 per cent of total cells. Folic acid was given to the patient later without further response.

Upon discharge the patient ceased taking vitamin B_{12} but continued to take folic acid orally. In May 1954 he was readmitted with recurrent diarrhea, pallor, weakness and weight loss of 25 pounds. Erythrocytes numbered 3 million per cu. mm. of blood, the hemoglobin content was 12.0 gm. per 100 cc. and the hematocrit was 33 per cent. Mean corpuscular volume was 110 cu. microns, mean corpuscular hemoglobin 40 micromicrons and mean corpuscular hemoglobin concentration 36 per cent. The result of an oral glucose tolerance test was normal. Vitamin B_{12} was given, 30 micrograms daily, and the reticulocytes rose to 4.8 per cent with a slow rise in hemoglobin, erythrocytes and hematocrit. Upon administration of aureomycin, diarrhea abated.

The foregoing clinical observations relative to the relationship of bacteria to hematopoiesis justify a hypothesis that an abnormal bacterial flora in the stagnant area of intestine may interfere with the utilization of vitamin B_{12}, resulting in B_{12} deficiency and megaloblastic anemia. In order to test this hypothesis the fecal excretion method for determining the absorption of radioactive vitamin B_{12} was used in the three patients with intestinal anastomosis. After the amount of cobalt^{60}-B_{12} excreted in the stools was measured, the patients were given either aureomycin or achromycin and the tests repeated. Two tests were done during the period of antibiotic administration in Cases 2 and 3, and one test in Case 1.

The results show that each patient excreted most of the test dose. However, they differed from patients with pernicious anemia in that intrinsic factor had no effect on absorption. During the administration of the antibiotic there was a pronounced decrease in fecal excretion in each case (Chart 4). The decreased excretion (or *increased absorption*) was much greater than variations found to occur spontaneously when tests were repeated in the same patient under the same conditions. In 14 patients in whom repeated tests were carried out the greatest variation was 18 per cent.

DISCUSSION

An explanation for the increased absorption of vitamin B_{12} and for the hematologic response which may occur in megaloblastic anemia during aureomycin administration is that bacterial competition for vitamin B_{12} is decreased. The impaired absorption of radioactive vitamin B_{12} might be explained by bacteria absorbing B_{12}, and thus denying it to the body. In these circumstances the radioactivity

recovered would be largely contained in the bacteria passed out in the feces. Certain strains of E. coli have pronounced avidity for B_{12} even though it may not be a growth requirement for these strains.

Although this is a plausible explanation, others do exist and it is quite likely that the mechanism is more complex than simple bacterial competition. Further study will be required in order to clarify the matter.

An interesting similarity comes to mind between the megaloblastic anemia associated with intestinal stasis and that occurring with fish tapeworm (diphyllobothrium latum) infestation in Finland. In both diseases the clinical picture is identical with that of Addisonian pernicious anemia, yet free hydrochloric acid and intrinsic factor secretion are normal. The fish tapeworm anemia can be cured by getting rid of the worm, just as the megaloblastic anemia of intestinal stagnation can be cured by surgical correction of the underlying lesion or, apparently, by changing the bacterial flora with antibiotics. Finally, although the underlying factors causing the anemia (intestinal blind loop on the one hand, intestinal parasite on the other) are extremely common, vitamin B_{12} deficiency, leading to anemia, does not occur very often.

In the management of a patient with anemia caused by intestinal lesions it would seem logical to correct the anatomical abnormality surgically, but only if this appears to be technically simple. An injection of 30 micrograms of vitamin B_{12} once a month will control the deficiency which causes the anemia. In none of the three cases herein reported was it felt that operative correction of the intestinal abnormality was indicated.

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